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Forecasting the burden of advanced knee osteoarthritis over a 10-year period in a cohort of 60–64 year-old US adults

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SUMMARY

Objective: To forecast the burden of symptomatic knee osteoarthritis (OA) in the elderly US population over a 10-year horizon.
Design: Using a computer simulation model of the natural history and management of knee OA combined with population-based data from the 2008 US Census we projected the 10-year burden of knee OA among persons 60–64 years of age. Knee OA incidence and progression rates were derived from national cohorts and calibrated to published literature.
Results: Using national data we estimated that 13% of 14,338,292 adults 60–64 years old have prevalent symptomatic, radiographic knee OA. Among persons surviving the next decade, 20% will have symptomatic advanced (Kellgren–Lawrence [K–L] grade 3) or end-stage (K–L 4) knee OA. Prevalence of advanced knee OA will range from 10% among non-obese to 35% among obese persons. Our estimates show that a more sensitive imaging tool, such as magnetic resonance imaging (MRI), may increase the number of OA cases diagnosed by up to 94% assuming that 50% of all 'pre-radiographic knee OA' (K–L 1) has some evidence of cartilage degeneration seen on MRI.
Conclusions: Projecting new and advanced cases of knee OA among persons aged 60–64 years over the next decade creates a benchmark that can be used to evaluate population-based benefits of future disease-modifying OA drugs that are currently undergoing testing at various stages.

Introduction

Knee osteoarthritis (OA) is a debilitating disorder that primarily affects older adults. Approximately 12–16% of US adults older than 60 years of age suffer from symptomatic knee OA[1,2]. A growing body of evidence suggests that obesity is a salient risk factor for knee OA incidence and may play a role in the disease's symptomatic progression[3–6]. Often working in concert with other risk factors, obesity exacerbates OA incidence risk through mechanical load and, likely, through metabolic pathways[7,8].

In the US, the obesity epidemic and aging baby-boomer population augur accelerated rates of knee OA incidence[9]. This increasing volume of OA cases may also be accompanied by an increased utilization of pharmaceutical and surgical interventions[10–12]. In addition, if more sensitive diagnostic tools such as magnetic resonance imaging (MRI) are implemented in OA diagnosis, rates of OA diagnosis can be expected to rise.

Our objective was to estimate the 10-year cumulative incidence and progression rates of knee OA in a defined population of persons aged 60–64 years. Long-term estimates for knee OA burden using current treatments will serve as benchmarks against which the population-based impact of newly developed disease-modifying regimens could be evaluated. Projections will inform clinicians and policy makers in evaluating the capacity of the

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health care system to address the growing epidemic of obesity and knee OA.

Methods

Analytic overview

We used the Osteoarthritis Policy (OAPol) Model to estimate the cumulative incidence rates of symptomatic advanced or end-stage knee OA over a 10-year time horizon in a population of persons aged 60–64 with demographic and obesity profiles similar to the general US population. Cohort characteristics were obtained from the Centers for Disease Control and Prevention (CDC) 2008 projections of the US 2000 Census, from the Third National Health and Nutrition Examination Survey (NHANES III), and from the NHANES 2007–2008[13–16]. Cumulative incidence of symptomatic advanced or end-stage knee OA was defined as the proportion of the original cohort alive at the 10-year follow-up with symptomatic advanced (Kellgren–Lawrence [K–L] 3) or end-stage (K–L 4) knee OA. Cumulative incidence rates were estimated separately for obese and non-obese persons. We forecast additional diagnosable cases of knee OA by expanding the definition of knee OA to encompass pre-radiographic OA (K–L 1) using MRI. To estimate the burden of disability among those affected by knee OA we applied data from 2005 to 2008 NHANES data on functional disability, defined as difficulty in walking and kneeling, for individuals between 70 and 74 years of age with OA, reflecting the study population 10 years from baseline.

The OAPol Model

The OAPol Model is a state transition, computer simulation model of the natural history of knee OA that runs on an annual cycle. "State transition" refers to the fact that the model characterizes each person's history as a sequence of annual transitions from one health state to another. Annual transition probabilities used in the OAPol model, derived from published data or secondary data analyses, are presented in Table I. Health states are chosen to describe the individual's current health, including the number of comorbidities, obesity status and knee OA status. They are designed to be predictive of comorbidities and mortality. The model defines four general health state categories: knee OA- and obesity-free, knee OA only, obesity only, knee OA and obesity. Throughout most of their lives, patients reside in one of these chronic states. Death can occur in any state.

The OAPol Model utilizes the K–L scale to define OA severity: K–L 0 (normal radiograph) is defined as 'no OA,' K–L 1 (questionable osteophytes) as 'pre-radiographic OA,' K–L 2 (definite osteophytes) as 'early OA,' K–L 3 (<50% narrowing of knee joint space) as 'advanced OA,' and K–L 4 (≥50% narrowing of joint space) as 'end-stage OA'. Symptomatic knee OA is defined as the concomitant presence of radiographic knee OA and knee pain on most days.

The OAPol Model tracks subjects' life courses until death. Over their life spans, subjects without knee OA are at risk for developing OA and subjects with the disease are at risk for progressing to more advanced stages based on subjects' current K–L grade and obesity, as defined by body mass index (BMI).

Knee OA incidence and progression rates in the OAPol Model are stratified by obesity and sex. Incidence is further stratified by age and progression is further stratified by K–L grade. At the beginning of a simulation, subjects are assigned a K–L grade and symptom status, based on their age and BMI. During each model cycle (1 year), subjects may develop knee OA if they are currently OA-free or progress by one K–L grade if they already have OA. For example, a subject with symptomatic early OA (K–L 2) at baseline surviving to the following year may be assigned one of two states: (1)

Table I
OAPOL Model input parameters

Parameter					Estimate
Mean age*					62.00 ± 0.67
BMI† Mean ± standard deviation (kg/m^2)					
Non-obese					25.00 ± 0.67
Obese					32.50 ± 0.67
% Female[13]					52.02
Race distributions for the US population by sex[13]			Female (%)		Male (%)
African American non-Hispanic			10.83		9.22
Caucasian Hispanic			8.40		8.21
Caucasian non-Hispanic			80.77		82.56
Comorbidity		Prevalence[17] (%)	Annual incidence[17] (%)		Relative risk of mortality[18,19,36]
Diabetes mellitus		7.20–37.28	0.29–7.20		1.00
Coronary heart disease		3.84–27.17	0.16–8.65		1.00–3.56
Cancer		1.77–8.68	0.10–3.33		1.00–17.32
Chronic obstructive pulmonary disorder		8.83–16.51	0.38–3.07		1.00
Musculoskeletal disorders other than OA		23.96–46.52	1.46–17.42		1.00
Obesity (30 kg/m^2 ≤ BMI)‡		User-defined	0		1.19–2.85
Knee OA incidence and progression estimates (annual probability, %)					
Sex	Obesity	Age group	Incidence[16,20,25] (95% CI)	Progression K–L 2–3[2,5] (95% CI)	Progression K–L 3–4[2,5] (95% CI)
Females	Non-obese	60–64	0.18 (0.09, 0.35)	4.00	1.95
		65–74	0.44 (0.23, 0.83)	(2.18, 5.97)	(0.39, 5.67)
	Obese	60–64	0.42 (0.21, 0.84)	8.95	4.27
		65–74	1.05 (0.56, 1.99)	(4.95, 13.19)	(0.87, 12.16)
Males	Non-obese	60–64	0.16 (0.08, 0.33)	5.58	1.29
		65–74	0.31 (0.16, 0.59)	(3.06, 8.30)	(0.26, 3.80)
	Obese	60–64	0.39 (0.19, 0.78)	12.26	2.94
		65–74	0.74 (0.38, 1.42)	(6.83, 17.90)	(0.60, 8.48)

* Mean age and standard deviation defined by user for analyses.
† Mean BMIs and standard deviations defined by user for analyses.
‡ Obesity prevalence determined by the user's definition for mean BMI distribution. Obesity progression was derived from NHANES 2007–2008 as a formula dependent on subject's age, race/ethnicity and sex.

symptomatic early OA (where they started), or (2) symptomatic advanced OA (K–L 3).

Competing risks for mortality are accounted for in the OAPol Model by incorporating several major comorbidities including cardiovascular disease, diabetes, chronic obstructive pulmonary disorders and malignancies. Comorbidity prevalence and incidence rates, stratified by age, sex, race/ethnicity and obesity state (non-obese, obese, and morbidly obese), were derived using NHANES III data and the US 2000 life tables[17,18] (Table I). Subjects that develop comorbidities may have a greater annual mortality risk. Excess mortality attributable to specific comorbidities is estimated from published literature and CDC national statistics[14,18,19]. The life expectancy derived from the OAPol Model approximates the life expectancy derived from CDC data with a high degree of accuracy, with differences for a baseline population of 60–64 years of age not exceeding 0.5 years[18].

Cohorts under consideration

We considered several hypothetical cohorts defined by a specific combination of three conditions at baseline: symptom status (asymptomatic vs symptomatic), obesity status (non-obese: BMI < 30 kg/m^2 vs obese: BMI ≥ 30 kg/m^2) and K–L grade (1–4) for a population cohort of individuals 60–64 years of age at baseline. We followed each of these cohorts over a 10-year time span estimating the number of newly developed or progressed to advanced or end-stage level knee OA cases among 10-year survivors.

Data sources

Model input parameters and transition probabilities are presented in Table I.

The size of the US population aged 60–64 years old was obtained from the US Census Bureau's 2008 population annual estimates[13]. NHANES III and NHANES 2007–2008 data were combined to determine the demographic characteristics of this population stratified by all permutations of obesity, symptom status and degree of radiographic OA severity. The radiographic knee OA data (K–L 0 to K–L 4) at baseline were derived from NHANES III data, as knee OA-related data were not available in the NHANES 2007–2008, while radiographs were performed from 1991 to 1994 for all NHANES III participants aged 60+[15,16]. Age/sex/race/obesity stratified prevalence rates for comorbidities used in the OAPol model (obesity, diabetes, coronary heart disease, malignancies, non-OA musculoskeletal disorders, and chronic obstructive pulmonary disorder) were derived from NHANES III data[17].

We derived annual symptomatic knee OA incidence from published data and progression rates using data from the Johnston County Osteoarthritis Project, a prospective population-based study of knee OA incidence and progression in Caucasians and African-Americans in North Carolina. The details of this study have been published elsewhere[20,2]. The OAPol Model's knee OA progression matrix contains flexible components that enable calibration of progression parameters used in the model to published data or independent cohorts. To derive base case progression estimates we calibrated the 5-year cumulative knee OA progression estimates obtained from the Johnston County Osteoarthritis Project to 5-year cumulative rates reported in a prospective population-based study by Cooper *et al.*[5]. Transition probabilities of knee OA progression stratified by obesity and K–L grade are presented in Table I.

Analysis assumptions

Based on published literature assessing population need for and willingness to undergo total knee replacement (TKR), we assumed that approximately 33% of the population with symptomatic end-stage (K–L 4) knee OA would elect TKR. This assumption is based on population-based estimates of willingness to undergo TKR documented by Hawker and colleagues[21]. To further substantiate this assumption, we calibrated the rates of offer and acceptance of TKR among eligible simulated patients in the model with observed rates of TKR utilization in the US.

To evaluate the implications of a new OA definition where some pre-radiographic knee OA is detectable by more sensitive imaging techniques, we assumed that 50% of 'pre-radiographic OA' (for which we used K–L 1 as a proxy) would be observable by MRI and diagnosed as 'early OA'.

Sensitivity analyses

To examine the robustness of our projections to variability in model input parameters we conducted several sensitivity analyses. To account for uncertainty, we conducted sensitivity analyses using the lower and upper 95% confidence intervals of incidence and progression rate estimates.

We examined the effect on our projections of increasing or decreasing the difference in incidence and progression of knee OA between obese and non-obese individuals by 50%. We also varied the percent of the population with K–L 4 symptomatic knee OA receiving TKR from 22% to 44%.

Next, we defined 'less conservative' and 'more conservative' case scenarios considering knee OA incidence and progression estimates obtained from different cohorts. Incidence and progression rates corresponding to Framingham Osteoarthritis Study (FOS) data led to the most conservative projections and were referred to as the 'more conservative' scenario[22]. The 'less conservative case' (highest rates of knee OA progression) scenario was based on estimates directly obtained from the Johnston County Osteoarthritis Project, which was characterized by a larger proportion of racial and ethnic minorities, a rural population, and a BMI greater than the national average[2].

The final round of sensitivity analyses was focused on varying the definition of early OA by varying the proportion of K–L 1 patients diagnosed with pre-radiographic OA from 0% to 100%.

Results

Projecting knee OA burden in an overall population of adults 60–64 years of age

Applying the NHANES-derived obesity distributions to the Census 2008 population size, we estimated the size of the US population 60–64 years old (Caucasian or African American race, Hispanic or non-Hispanic ethnicity) to be 14,338,292 persons[13,16,17]. Of these adults, about 43% are obese and 33% have evidence of radiographic knee OA (K–L $\geq$2) (Table II).

We estimated that 80% of obese and 86% of non-obese adults would survive 10 years beyond the baseline. Of the surviving adults, 20%, or 2,442,582 individuals, will have symptomatic advanced or end-stage knee OA. These estimates are derived assuming 33% of adults with symptomatic end-stage knee OA elect TKR, resulting in disease 'resolution'[21]. Ten percent (689,996 adults) of the surviving non-obese population compared with 35% (1,752,586 adults) of the surviving obese population will have symptomatic advanced or end-stage knee OA.

Among obese adults free of radiographic knee OA at the baseline, the estimated rates of advanced or end-stage knee OA range from 2% of those alive at year 10 for obese to 0.4% among non-obese adults. Obese adults with early OA (K–L 2) at baseline have an estimated 63% 10-year risk of developing symptomatic advanced or

Table II
10-year projected burden of symptomatic advanced and end-stage knee OA in the US population 60–64 years of age at baseline

Baseline K–L state	Baseline obesity status	Baseline N	10-year results	
			% Survived (# of survivors)	% Survived with symptomatic K–L 3 or 4 knee OA (#)
0, 1 (no evidence of radiographic OA)	Non-obese	6,440,155	86% (5,515,796)	0.43% (23,447)
	Obese	3,161,947	80% (2,528,756)	2% (48,682)
2 (Early OA)	Non-obese	1,361,985	86% (1,166,498)	37% (434,806)
	Obese	2,032,076	80% (1,625,146)	63% (1,016,117)
3 (Advanced OA)	Non-obese	206,888	86% (177,193)	95% (168,283)
	Obese	762,285	80% (609,635)	90% (547,203)
4 (End-stage OA)	Non-obese	110,589	86% (94,716)	67% (63,460)
	Obese	262,366	80% (209,826)	67% (140,584)
Overall population		14,338,292	83% (11,927,566)	20% (2,442,582)
Non-obese		8,119,617	86% (6,954,204)	10% (689,996)
Obese		6,218,675	80% (4,973,362)	35% (1,752,586)

end-stage knee OA, a risk 1.68 times greater than the non-obese population's risk of 37%.

Projecting disability burden due to symptomatic knee OA

Data from the NHANES 2007–2008 revealed that disability burden ranges from 46% for obese to 39% for non-obese persons aged 70–74 with symptomatic knee OA. Applying these data to our model-based estimates suggested that 8% of the population cohort of individuals 60–64 years of age surviving 10 years will experience substantial disability due to symptomatic knee OA. These estimated rates vary from 4% in non-obese to 16% in obese persons.

Sensitivity analyses

'More conservative case' and 'less conservative case' scenarios

The 'more conservative case' scenario considering progression rates consistent with the FOS resulted in a 10-year cumulative incidence of knee OA of 16%, compared to 20% projections based on the base case. Estimates corresponding to the 'less conservative case' scenario, using Johnston County Osteoarthritis Project progression rates, resulted in a higher rate of symptomatic advanced or end-stage knee OA of 23% (Fig. 1).

Projecting 10-year incidence of knee OA with a 'pre-radiographic OA' definition

At baseline, 6,975,762 individuals aged 60–64 were knee OA free. Of the 5,884,697 survivors 10 years from baseline, 1.2% will develop OA detectable by traditional radiographic methods. Assuming 50% of 'pre-radiographic OA' subjects are diagnosed as 'early OA', the number of OA cases will almost double, reaching 139,844 cases (2.4% of survivors). When the proportion of K–L 1 patients diagnosed with 'pre-radiographic OA' is increased from 50% to 100%, the total number of diagnosed cases at 10 years will increase by a factor of 1.5 to 207,467.

Varying parameters affecting progression

Altering knee OA incidence and progression rates for obese individuals relative to those of non-obese persons influenced the total burden of OA. Decreasing and increasing the incidence and progression rates of knee OA by 50% of the difference between obese and non-obese persons resulted in 10-year estimates of

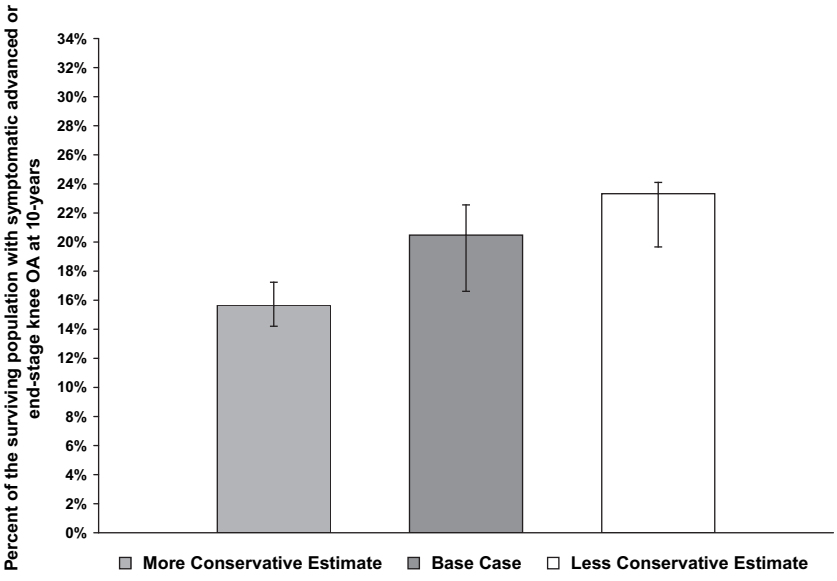

Fig. 1. Percent of the surviving baseline population with symptomatic advanced or end-stage knee OA at 10 years in the 'base case' scenario, the OAPol Model incidence and progression rates were calibrated to rates reported by Cooper *et al.* (light grey)[5]. In the 'more conservative case' (dark grey) and 'less conservative case' (white) scenarios, the OAPol Model incidence and progression rates were calibrated to FOS and Johnston County Osteoarthritis Project data, respectively[22,2]. The height of each bar depicts the percent of the overall population with symptomatic advanced (K–L 3) or end-stage (K–L 4) knee OA 10 years from the baseline. The uncertainty in progression and incidence parameter estimates are depicted by error bars. The asymmetry of the error bars reflects utilization of TKR.

symptomatic advanced or end-stage knee OA rates of 19% and 22%, respectively (base case was 20%).

Varying the percent of subjects with symptomatic end-stage knee OA that received TKR from 22% to 44% had minimal effects on model projections of OA volume. Assuming 22% of the population with symptomatic end-stage knee OA elects TKR, 21% (2,524,770 individuals) of the subjects alive at 10 years and 27% (2,032,554 individuals) of the subjects alive at 20 years will have symptomatic advanced or end-stage knee OA. Assuming 44% of the population with symptomatic end-stage knee OA elects TKR, 20% (2,360,395 individuals) of the subjects alive at 10 years will have symptomatic advanced or end-stage knee OA.

Discussion

This is the first study to project the cumulative incidence of knee OA in the US population aged 60–64 and estimate the effects of obesity on incidence and progression of knee OA over 10 years. Results of our projections revealed that among the 14.3 million US adults aged 60–64, as defined by 2008 Census population estimates, 10 years from the baseline 11.9 million will still be alive and 2.4 million of these survivors will have symptomatic advanced or end-stage knee OA.

Our study illustrates and quantifies the relative impact of the higher risk on knee OA development among obese individuals over a 10-year time horizon from the population perspective. We limited our projections to a 10-year time horizon as longer time spans may have more limited value due to the likely development of new therapies with structure-modifying properties. These estimates and other well-established risks of obesity support ongoing public health efforts to educate non-obese and obese adults about the importance of weight management. Helping adults achieve and maintain a healthy BMI will significantly reduce the incidence of new OA cases.

Several prospective population-based studies note a relationship between obesity and rates of OA incidence and/or progression[4,5,23–29]. Following the FOS Cohort, investigators demonstrated that obesity not only precedes onset of knee OA, but also increases risk for incident OA by an odds ratio of 3.8/2 kg increase in baseline BMI over 8 years[23]. In a separate analysis, investigators showed that a subset of women (in the FOS cohort) who lost approximately 5 kg over 10 years were half as likely to develop symptomatic knee OA[29]. Further, investigators found that obesity and morbid obesity in the Multicenter Osteoarthritis Study (MOST) Cohort increased patient risk for incident knee OA by factors of 2.4 and 3.2 respectively[25].

In another projection study, Murphy *et al.* predicted that the lifetime risk of developing OA in the Johnston County Osteoarthritis Project Cohort was 44.7%[30]. Though we based our projections on progression estimates from the Johnston County Osteoarthritis Project in the OAPol Model, our baseline OA prevalence distributions came from the US population, not the Johnston County Cohort. In addition, our outcome measure, symptomatic advanced and end-stage knee OA (K–L 3 or K–L 4 with symptoms), was less inclusive than the measure used by Murphy *et al.* (K–L 2+ with symptoms). These differences make our 10-year projection of symptomatic advanced or end-stage knee OA difficult to directly compare with Murphy *et al.'s* projection of 44.7%. Both these studies, however, indicate that obesity augments lifetime risk for knee OA by a factor of at least two.

By using a computer simulation model, we project cumulative rates of symptomatic advanced and end-stage knee OA in a national sample of US citizens 60–64 years of age, fully accounting for all sources of mortality and eliminating uncertainty due to loss to follow-up, pertinent to many population-based cohorts. The modest difference in the estimated proportion of the population with OA at baseline and after 10 years is due primarily to the fact that persons with OA are more likely to be obese and therefore have lower life expectancy.

Our projections should be considered within the scope of several limitations. Our analysis was restricted to a population cohort aged 60–64 years at the baseline, which in 10 years reached 70–74 years of age. Were a similar simulation for other age groups in the population to be added, increases in the expected number of OA cases would be greater. Specifically, if we extended the analyses to subjects 70–74 years old at baseline, mortality would be much higher, and the proportion of survivors developing OA over a 10-year timeframe would also be considerably higher. The population-based implications are highest for the 60–64-year age group.

We made the assumption that the obesity status of adults aged 60–64 does not change over time. While we used published data to account for small fluctuations in BMI, obesity status, defined by BMI$\geq$30 kg/m^2 remained stable. A large volume of data suggests that fluctuations in BMI occur mostly between 25 and 55 years of age, and by age 60 BMI remains relatively stable[31]. Therefore, we did not model changes in BMI in this population. Following subjects in the NHANES, investigators found that US adults aged 55–64 and 65–74 at the baseline (1971–1975) had on average lost 0.3–0.5 and 1.1–1.7 BMI units (kg/m^2) respectively by the 10-year follow-up (1981–1984)[32]. We acknowledge that some obese individuals simulated by the OAPol Model may have been categorized as non-obese at the 10-year follow-up points had they lost up to 1.7 BMI units. Finally, recent studies have suggested that the effect of BMI on rates of knee OA progression is modified by knee alignment[25,33,34]. Because the OAPol Model progression rates were derived from population-based studies, our obese and non-obese progression rates are weighted averages for those with varying degrees of malalignment. The specifics of the interaction between malalignment and obesity, however, are beyond the scope of this analysis. We recognize as well that our binary categorization of obesity status (BMI $<$ 30 vs $\geq$30) may obscure associations between obesity, incidence and progression. In fact, the risk for progression to TKR increased with increasing BMI, even within the non-obese range[24]. However, available data on BMI-stratified OA structural progression limited us to a somewhat crude (binary) level of granularity.

We used K–L 1 as a proxy for 'pre-radiographic OA' acknowledging that the detection of a questionable osteophyte (the definition of K–L 1) may have little bearing on MRI diagnosis of early osteoarthritic changes (such as cartilage defects that are not visible on radiographs). Our rationale is that patients with K–L 1 are known to be at a greater risk of development of incident early OA (K–L 2), suggesting that K–L 1 is indeed an early OA state[5,35]. Our findings document the large increase in incidence and prevalence of OA that would result from using MRI to identify early OA. We suggest that in the absence of therapeutic interventions that would delay progression (such as a structure-modifying agent), a large increase in the number of patients diagnosed with OA would likely lead to more utilization of imaging, physician visits and other resources, without obvious structural benefit for the patient. Such increases in health care utilization will lead to further increases in health care expenditures, without clear evidence of justification of such expenses.

Our sensitivity analyses showed that altering progression rates has a modest impact on the cumulative incidence of symptomatic advanced and end-stage knee OA. The calibration and validation of 8-year OAPol Model incidence and progression elements demonstrated that the progression rates used for our main analyses were comparable to rates found in real US cohorts[22,23]. In addition, our calibration of the OAPol Model to data from the FOS provided more conservative incidence estimates, while our calibration of the model to original Johnston County Project data provided more

liberal estimates. Differences in the rates of knee OA incidence and progression used in this analysis may be attributed in part to differences in study sample populations. Subjects in the Johnston County Project were more racially diverse (81.5% Caucasian and 18.5% African American), had a higher average BMI, were more likely to live in rural areas, and were younger, on average, than subjects followed in the FOS Cohort[2,23].

In summary, 20% of the surviving cohort or 17% of the baseline population cohort, totaling 2.4 million adults aged 60–64 at baseline, will have symptomatic advanced or end-stage OA in 10 years. Obesity greatly augments patient risk for incident and progressive knee OA. More sensitive imaging tools may lead to higher health care utilization. Retarding the onset of OA by preventative obesity control is likely to yield the greatest economic and patient health gains. Effective and sustainable weight management plans may delay OA incidence and reduce the risk for a host of associated and costly chronic conditions including diabetes and heart disease.

Author contributions

Conception and design: Holt, Losina.

Analysis and interpretation of the data: Holt, Katz, Hunter, Jordan, Losina, Gerlovin.

Drafting of the article: Holt, Losina.

Critical revision of the article for important intellectual content: Katz, Hunter, Jordan, Gerlovin, Reichmann, Kessler, Losina, Wright.

Final approval of the article: Holt, Katz, Hunter, Jordan, Gerlovin, Reichmann, Kessler, Losina, Wright.

Provision of study materials or patients: Jordan, Losina.

Statistical expertise: Reichmann, Wright, Losina.

Obtaining of funding: Losina.

Collection and assembly of data: Holt, Jordan, Reichmann, Wright.

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Conflict of interest

Authors do not have any conflict of interest with respect to the context of this paper.

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